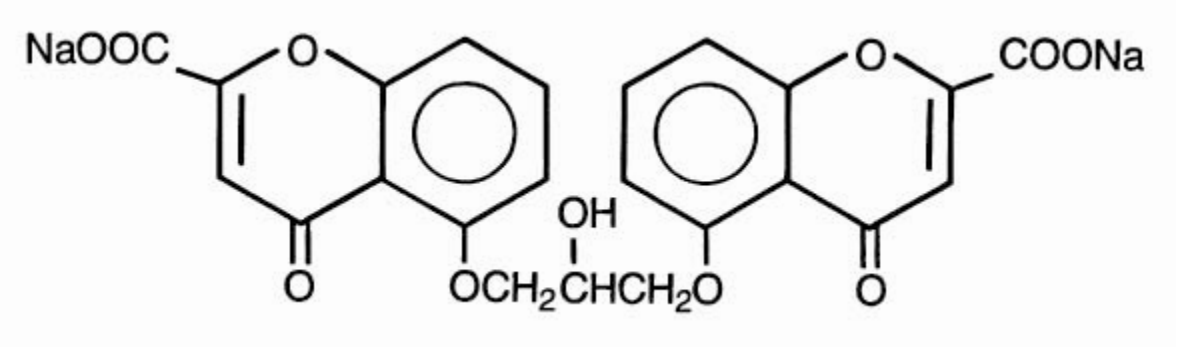
INTAL - cromolyn sodium inhalant
King Pharmaceuticals, Inc.

For Oral Inhalation Only
Rx only

DESCRIPTION

The active ingredient of **Intal** Inhaler is cromolyn sodium, USP. It is an inhaled anti-inflammatory agent for the preventive management of asthma. Cromolyn sodium is disodium 5, 5'-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate]. The empirical formula is $C_{23}H_{14}Na_2O_{11}$; the molecular weight is 512.34. Cromolyn sodium is a water soluble, odorless, white, hydrated crystalline powder. It is tasteless at first, but leaves a slightly bitter aftertaste. The molecular structure of cromolyn sodium is:



Intal Inhaler (cromolyn sodium inhalation aerosol) is a metered dose aerosol unit for oral inhalation containing micronized cromolyn sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each actuation delivers approximately 1 mg cromolyn sodium from the valve and 800 mcg cromolyn sodium through the mouthpiece to the patient. Each 8.1 g canister delivers at least 112 metered inhalations (56 doses); each 14.2 g canister delivers at least 200 metered inhalations (100 doses).

CLINICAL PHARMACOLOGY

In vitro and *in vivo* animal studies have shown that cromolyn sodium inhibits sensitized mast cell degranulation which occurs after exposure to specific antigens. Cromolyn sodium acts by inhibiting the release of mediators from mast cells. Studies show that cromolyn sodium indirectly blocks calcium ions from entering the mast cell, thereby preventing mediator release.
Cromolyn sodium inhibits both the immediate and non-immediate bronchoconstrictive reactions to inhaled antigen. Cromolyn sodium also attenuates bronchospasm caused by exercise, toluene diisocyanate, aspirin, cold air, sulfur dioxide, and environmental pollutants, at least in some patients.
Cromolyn sodium has no intrinsic bronchodilator or antihistamine activity.
After administration of cromolyn sodium capsules by inhalation, approximately 8% of the total dose administered is absorbed and rapidly excreted unchanged, approximately equally divided between urine and bile. The remainder of the dose is either exhaled or deposited in the oropharynx, swallowed, and excreted via the alimentary tract.

INDICATIONS AND USAGE

Intal Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.
In patients whose symptoms are sufficiently frequent to require a continuous program of medication, **Intal** Inhaler is given by inhalation on a regular daily basis. (See **DOSAGE AND ADMINISTRATION**.) The effect of **Intal** Inhaler is usually evident after several weeks of treatment, although some patients show an almost immediate response.
If improvement occurs, it will ordinarily occur within the first 4 weeks of administration as manifested by a decrease in the severity of clinical symptoms of asthma, or in the need for concomitant therapy, or both.
In patients who develop acute bronchoconstriction in response to exposure to exercise, toluene diisocyanate, environmental pollutants, known antigens, etc., **Intal**Inhaler should be used shortly before exposure to the precipitating factor, i.e., within 10 to 15 minutes but not more than 60 minutes. (See **DOSAGE AND ADMINISTRATION**.) **Intal** Inhaler may be effective in relieving bronchospasm in some, but not all, patients with exercise induced bronchospasm.

CONTRAINDICATIONS

Intal Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other ingredients in this preparation.

WARNINGS

Intal Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. Intal Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS

General

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg/day three days per week), hamsters (intraperitoneal administration at doses up to 53 mg/kg/day three days per week for 15 weeks followed by 17.5 mg/kg/day three days per week for 37 weeks), and rats (18 months subcutaneous treatment at doses up to 75 mg/kg/day six days per week) showed no neoplastic effects. These doses in mice, hamsters, and rats correspond to approximately 40, 10, and 80 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis, or, approximately 20, 5, and 40 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis.

Cromolyn sodium showed no mutagenic potential in Ames Salmonella/microsome plate assays, mitotic gene conversion in *Saccharomyces cerevisiae*, and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 220 and 130 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis.

Pregnancy

Pregnancy Category B: Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg/day and 160 mg/kg/day, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg/day produced no evidence of fetal malformations. These doses represent approximately 340, 210, and 1,200 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, **Intal** Inhaler should be used during pregnancy only if clearly needed.

Drug Interactions During Pregnancy

Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses up to 540 mg/kg/day (approximately 340 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg/day (approximately 7 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) increased both resorptions and malformations. The addition of 540 mg/kg/day of cromolyn sodium (approximately 340 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) to 2.7 mg/kg/day of isoproterenol (approximately 7 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers

It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when **Intal** Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 5 years have not been established. For young pediatric patients unable to utilize the Inhaler, **Intal** Nebulizer Solution (cromolyn sodium inhalation solution, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of **Intal** Inhaler is particularly important in pediatric patients.

Geriatric Use
Clinical studies of **Intal** Inhaler did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS
In controlled clinical studies of **Intal** Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were:

Throat irritation or dryness

Bad taste

Cough

Wheeze

Nausea

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation, and wheezing.
Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.
The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomachache, polymyositis, vertigo, and liver disease.

OVERDOSAGE
There is no clinical syndrome associated with an overdosage of cromolyn sodium. In several animal species acute toxicity with cromolyn sodium occurs only with very high exposure levels. No deaths occurred at the highest oral doses tested in mice, 8000 mg/kg (approximately 5100 and 2700 times the maximum recommended daily inhalation doses in adults and children, respectively, on a mg/m^2 basis) or in rats, 8000 mg/kg (approximately 10,000 and 5400 times the maximum recommended daily inhalation doses in adults and children, respectively, on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION
For management of bronchial asthma in adults and pediatric patients (5 years of age and over) who are able to use the Inhaler, the usual starting dosage is two metered inhalations four times daily at regular intervals. This dose should not be exceeded. Not all patients will respond to the recommended dose and there is evidence to suggest, at least in younger patients, that a lower dose may provide efficacy.
Patients with chronic asthma should be advised that the effect of **Intal** Inhaler therapy is dependent upon its administration at regular intervals, as directed. **Intal** Inhaler should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared, and the patient is able to inhale adequately.
For the prevention of acute bronchospasm which follows exercise, exposure to cold, dry air, or environmental agents, the usual dose is two metered inhalations shortly before exposure to the precipitating factor, i.e., within 10 to 15 minutes but not more than 60 minutes.
Intal Inhaler Therapy in Relation to Other Treatments for Asthma:*Non-steroidal agents:***Intal** Inhaler should be *added* to the patient's existing treatment regimen (e.g., bronchodilators). When a clinical response to **Intal** Inhaler is evident, usually within two to four weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.
If concomitant medications are eliminated or required on no more than a prn basis, the frequency of administration of **Intal** Inhaler may be titrated downward to the lowest level consistent with the desired effect. The usual decrease is from two metered inhalations four times daily to three times daily to twice daily. It is important that the dosage be reduced gradually to avoid exacerbation of asthma. It is emphasized that in patients whose dosage has been titrated to fewer than four inhalations per day, an increase in the dosage of **Intal** Inhaler and the introduction of, or increase in, symptomatic medications may be needed if the patient's clinical condition deteriorates.
Corticosteroids: In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of **Intal** Inhaler. If the patient improves, an attempt to decrease corticosteroids should be made. Even if the corticosteroid-dependent patient fails to show symptomatic improvement following **Intal** Inhaler administration, the potential to reduce corticosteroids may nonetheless be present. Thus, gradual tapering of corticosteroid dosage may be attempted. It is important that the dose be reduced slowly, maintaining close supervision of the patient to avoid an exacerbation of asthma.

It should be borne in mind that prolonged corticosteroid therapy frequently causes an impairment in the activity of the hypothalamic-pituitary-adrenal axis and a reduction in the size of the adrenal cortex. A potentially critical degree of impairment or insufficiency may persist asymptomatically for some time even after gradual discontinuation of adrenocortical steroids. Therefore, if a patient is subjected to significant stress, such as a severe asthmatic attack, surgery, trauma, or severe illness while being treated or within one year (occasionally up to two years) after corticosteroid treatment has been terminated, consideration should be given to reinstituting corticosteroid therapy. When respiratory function is impaired, as may occur in severe exacerbation of asthma, a temporary increase in the amount of corticosteroids may be required to regain control of the patient's asthma.

It is particularly important that great care be exercised if for any reason cromolyn sodium is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids. In such cases, continued close supervision of the patient is essential since there may be sudden reappearance of severe manifestations of asthma which will require immediate therapy and possible reintroduction of corticosteroids.

For best results, the canister should be at room temperature before use.

HOW SUPPLIED

Intal Inhaler is supplied as an aerosol canister which provides 112 metered dose actuations from the 8.1 gram inhaler and 200 metered dose actuations from the 14.2 gram inhaler. The correct amount of medication in each inhalation cannot be assured after 112 actuations from the 8.1 gram canister or 200 actuations from the 14.2 gram canister even though the canister may not feel completely empty. The canister should be discarded when the labeled number of actuations have been used.

Each actuation delivers 1 mg cromolyn sodium through the valve and 800 mcg through the mouthpiece to the patient. The **Intal** Inhaler canister and accompanying mouthpiece are designed to be used together. The Intal Inhaler canister should not be used with other mouthpieces and the supplied mouthpiece should not be used with other products' canisters. **Intal** Inhaler is supplied with a white plastic mouthpiece with blue dust cap and patient instructions.

NDC 60793-011-14 ..... 14.2 g canister

NDC 60793-011-08 ..... 8.1 g canister

Store between 15° to 30°C (59° to 86°F). Contents under pressure. Do not puncture, incinerate, or place near sources of heat. Exposure to temperatures above 120°F may cause bursting. **Avoid spraying in eyes. Keep out of the reach of children.**

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

WARNING: Contains CFC-12 (dichlorodifluoromethane) and CFC-114 (dichlorotetrafluoroethane), substances which harm public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Information For The Patient" portion of this package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

Rx only

Intal® is a registered trademark of King Pharmaceuticals, Inc.

Distributed by: King Pharmaceuticals, Inc., Bristol, TN 37620

Manufactured by: Health Care Specialties Division, 3M Health Care Limited, Loughborough, England LE11 1EP

Made in United Kingdom.

Prescribing Information as of September 2005.

INFORMATION FOR PATIENTS

INTAL® INHALER (cromolyn sodium inhalation aerosol)

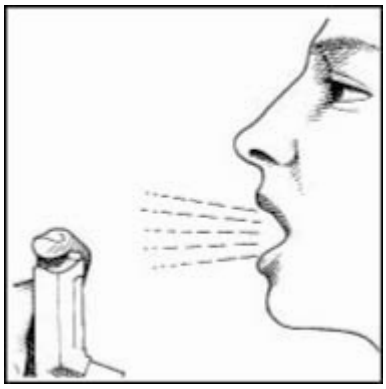
Metered Dose Inhaler

For Oral Inhalation Only

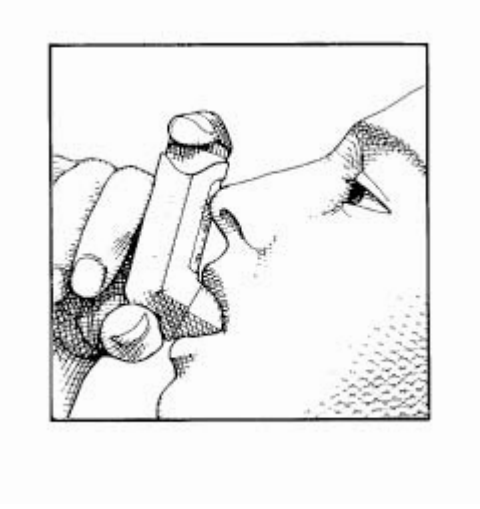
1. Make sure the canister is properly inserted into the Inhaler unit. Take the cover off the mouthpiece. **Shake the Inhaler gently.** If the mouthpiece cover is not present, the Inhaler should be inspected for the presence of foreign objects.

2. Hold Inhaler and breathe out slowly and fully, expelling as much air as possible. **Do not breathe into the Inhaler**– it could clog the Inhaler valve.

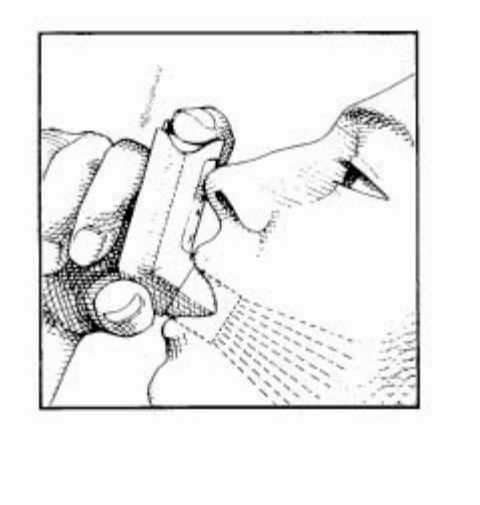
3. **Avoid spraying in eyes.**



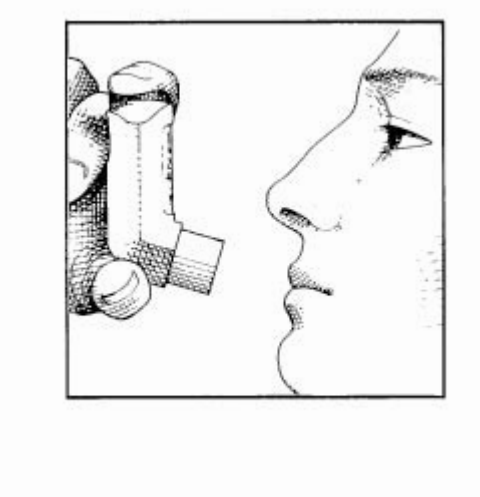
4. Place the mouthpiece into your mouth, close your lips around it, and tilt your head back. Keep your tongue below the opening of the Inhaler.



5. While breathing in deeply and slowly through the mouth, fully depress the top of the metal canister with your index finger.



6. Remove the Inhaler from your mouth. Hold your breath for several seconds, then breathe out slowly. This step is very important. It allows the **Intal** to spread throughout your lungs. Repeat steps 2-5, then replace the mouthpiece cover.



FOR BEST RESULTS

1. Before using the Inhaler for the first time, or if it has not been used for a while, it's a good idea to test it. Just give the canister one press.

2. It is essential that the canister be pressed at exactly the same time as you breathe in, so it's worth some time practicing this.

3. The dose delivered from the Inhaler can be seen as a fine white mist. If any of this can be seen escaping from your mouth or nose, then you are not using the Inhaler correctly.

4. To keep your Inhaler in good working order, do not exhale into mouthpiece.

5. Keep the cap on the Inhaler while not in use so that dirt can't get into it. You can clean the Inhaler by removing the metal canister and rinsing the plastic mouthpiece in warm water. (See **CLEANING** Instructions.)

6. The correct amount of medication in each inhalation cannot be assured after 112 actuations from the 8.1 gram canister or 200 actuations from the 14.2 gram canister even though the canister may not feel completely empty. You should keep track of the number of actuations used from each canister of **Intal** Inhaler and discard the canister after 112 actuations from the 8.1 gram canister or 200 actuations from the 14.2 gram canister. Before you reach the specified number of actuations, you should consult your physician to determine whether a refill is needed. Just as you should not take extra doses without consulting your physician, you also should not stop using **Intal** Inhalerwithout consulting your physician.

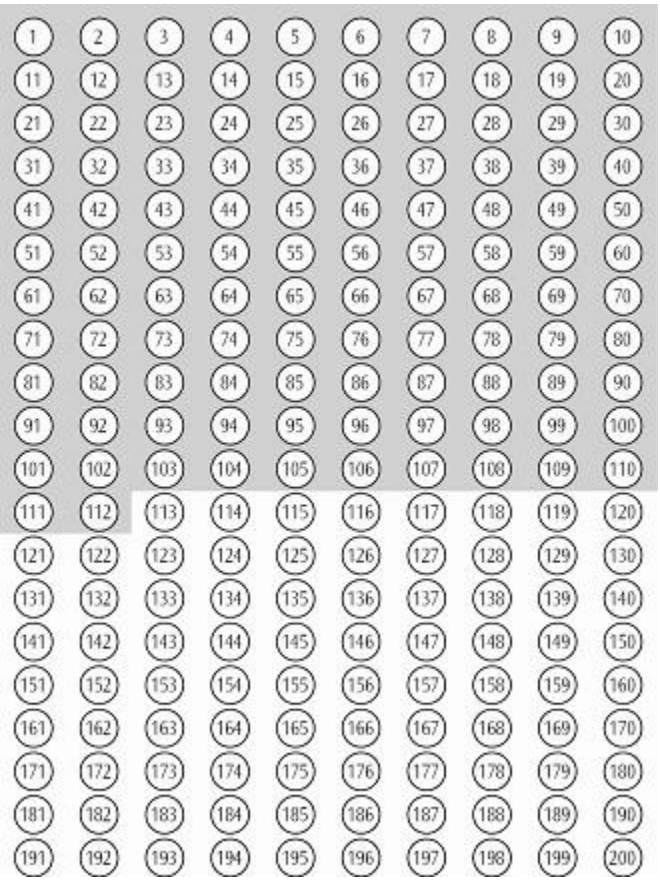
7. For optimal results, the canister should be at room temperature before use.

HOW TO CHECK CONTENTS OF YOUR CANISTER

Shaking the canister will NOT give you a good estimate of how much medication is left. We have included a convenient check-off chart to assist you in keeping track of medication inhalations used. This will help assure that you receive the labeled number of inhalations present.

Each 8.1 gram Inhaler delivers 112 metered inhalations
Each 14.2 gram Inhaler delivers 200 metered inhalations

Intal® Inhaler Check-Off Chart



- Retain with medication or affix to convenient location.

- Starting with inhalation #1, check off one circle for each inhalation used.

- **DISCARD MEDICATION AFTER THE LABELED NUMBER OF INHALATIONS HAVE BEEN USED**

- **NEVER IMMERSE THE METAL CANISTER IN WATER**

IMPORTANT: Remember— a little time spent taking **Intal** correctly and regularly can save you from countless attacks of asthma and the upheaval they cause.
It must be used every day as directed by your doctor. Do not stop the treatment or even reduce the dose without consulting your doctor.
The **Intal** Inhaler canister and accompanying mouthpiece are designed to be used together. The **Intal** Inhaler canister should not be used with other mouthpieces and the supplied mouthpiece should not be used with other products' canisters.
DOSAGE: For management of bronchial asthma in adults and children 5 years of age and older, the usual starting dosage is two metered inhalations four times a day at regular intervals. When asthma symptoms are well controlled, your doctor may reduce the dose to three times a day, and sometimes two times a day.
For prevention of acute bronchospasm which follows exercise, exposure to cold, dry air, or environmental agents, the usual dosage is two metered inhalations shortly **before exposure** to the offending factor.
Use as directed by your physician.
CLEANING: Twice a week, remove the metal canister from the plastic mouthpiece. Wash the mouthpiece in warm water and **dry thoroughly** before replacing the metal canister. **Never immerse the metal canister in water.**
STORAGE: Store between 15° to 30°C (59° to 86°F). Contents under pressure. Do not puncture, incinerate, or place near sources of heat. Exposure to temperatures above 120°F may cause bursting. **Keep out of the reach of children. Avoid spraying in eyes.**
Note: The indented statement below is required by the Federal Government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

This product contains CFC-12 (dichlorodifluoromethane) and CFC-114 (dichlorotetrafluoroethane), substances which harm the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN. If you have any questions about alternatives, consult with your physician.

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Prescribing Information as of September 2005.